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(57) Abstract

A pharmaceutical composition for use in the treatment of gastric disorders associated with *Helicobacter pylori* comprising an antimicrobial agent optionally co-administered with a release-delaying substance.

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PHARMACEUTICAL COMPOSITION FOR THE TREATMENT OF GASTRITIS

The present invention relates to pharmaceutical compositi ns of antimicrobial agents active against Helicobacter pylori and their use in the treatment of gastrointestinal disorders associated with Helicobacter pylori infection.

Helicobacter pylori (formerly known as Campylobacter pyloridis) is a spiral-shaped Gram-negative organism which appears to live beneath the mucus layer of the stomach. Many recent studies have shown an association between the presence of H.pylori in the gastric mucosa and histologically confirmed gastritis.

In the light of these results, it has been suggested that the organism may be a pathogen which causes, or at least exacerbates, gastritis, and may also be important in the aetiology of peptic ulceration. Reviews on the state of the art include those by C.A.M. McNulty in J. Infection, 1986, 13, 107-113, and by C.S. Goodwin et al. in J. Clin. Pathol., 1986, 39, 353-365.

H.pylori is known to be susceptible to a large number of antimicrobial agents *in vitro*. Furthermore, several workers have shown that treatment of gastritis with antimicrobial agents, for example β-lactam antibiotics such as amoxycillin, or bismuth salts, leads to eradication of the associated H.pylori organisms *in vivo*.

GB 2 243 549 A (Reckitt & Colman), published November 6, 1991, claims the use of the non-antibiotic antimicrobial agent triclosan for the preparation of a medicament for the treatment of gastrointestinal disorders associated with Helicobacter pylori infection. According to GB 2 243 549 A, the medicament may be formulated as a gastric sustained release composition having prolonged residence time within the stomach and continuously releasing triclosan during that time. Triclosan compositions formulated so as to produce floating alginate rafts within the stomach, or as muco-adherent coated granules or spheroids, are identified as suitable sustained release compositions.

GB 2 243 549 A further describes, for tablets, a co-formulation and, for tablet or liquid presentations, co-administration with a pharmaceutically acceptable

solid carboxylic acid, or salt thereof, in order to overcom the tendency for elevated stomach pH, observed with certain patients suffering from Helicobacter pylori infections, to reduce th ability for alginate rafts to float. Citric acid is referred to as a suitable acid for this purpose.

For comparative purposes, GB 2 243 549 A discloses the *in vitro* testing of 11 antimicrobial compounds in addition to triclosan versus Helicobacter pylori, based on methods described by McNulty et al. (Antimicrobial Agents & Chemotherapy, 28, 837-838, 1985). MIC results for triclosan, tinidazole, cetalkonium chloride, cetyl pyridinium chloride, clioquinol, hexetidine, dichlorophen, halquinol, 4-hexyl recorcinol, hibitane (chlorhexidine gluconate), PCMX (chorloxylenol), and guaiacol are disclosed.

J. Pediatr. Gastroenterol. Nutr., 9(1), 46-8, (1989), describes Helicobacter pylori as being extremely sensitive to the anti-infective activity of benzocaine, a commonly used topical anaesthetic.

It has now been found that activity against Helicobacter pylori is also conferred by a range of readily available substances, in particular substances which already have utililty as antimicrobial agents.

Included within this range of substances are groups of antimicrobial agents respectively defined as cationic antimicrobial agents, benzene derivatives, phenols, and amines, and certain naturally occuring substances, for example certain plant extracts.

Included within the group known as cationic antimicrobial agents are pyridinium and isoquinolinium compounds, guanides, for example bis-biguanides, and a range of quaternary ammonium salts. A number of cationic antimicrobial agents have shown activity against human oral bacteria which has promoted their use in the treatment or prophylaxis of periodontal diseases and dental caries.

Examples of substances which have now been found to have *in vitro* activity against strains f Helicobacter pylori resident in the gastric and duodenal mucosa, and hence to have potential utility for th *in vivo* treatment of gastric disorders associated with Helicobacter pylori, include benzene derivatives such as benzoic acid, benzyl alcohol, dibromopropamidine

isethi nate, 2,4-dichlorobenzyl alcohol, and hyroxy benzoates including methy-, thyl-, propyl-, n-butyl-, n-heptyl- and benzyl-p-hydroxy benzoates; phenols such as amylmetacresol, chlorochresol, phenol, trichlorophenol and creosote; amines such as hexamine; bis-biguanides such as chlorhexidine hydrochloride; quaternary ammonium compounds such as benzalkonium chloride, dequilinium chloride, domiphen bromide and cetrimide; pyrimidines such as hexetidine citrate; glycerol esters such as glycerol monolaurate; dyclonine hydrochloride; miconazole; mupirocin; polynoxylin; povidone iodine; sorbate; and natural products such as garlic and tea tree oil.

Accordingly, the present invention provides the use of these substances hereinbefore identified in the manufacture of a medicament for the treatment of gastric disorders associated with Helicobacter pylori.

It has been found that treatment of H.pylori associated gastritis with antimicrobial agents given by a conventional oral dosing regimen may require a prolonged course of therapy to be effective. Furthermore, follow-up of patients cleared of H.pylori infection by antimicrobial treatment has shown that relapse (rather than reinfection) can be a problem.

In another aspect of the invention, substances having activity against H. pylori may be formulated as gastric controlled release compositions, more especially as compositions which prolong residence time of the antimicrobial agent within the stomach.

Bioadhesive materials have received considerable attention as platforms for controlled drug delivery. They can be targetted to specific drug administration sites, prolong the residence time and ensure an optimal contact with the absorbing surface. Many different types of bioadhesive materials, both natural and synthetic, can be used in the design of controlled drug delivery systems.

Sucralfate, a basic aluminium sulphate sucrose complex, is an ulcer-preventing agent having anti-pepsin and antiacid properties. It has muco-adherent properties such that when administered orally it reacts with gastric juice to form a sticky paste which protects the mucosa by coating, and also binds to ulcer-affected sites. The preparation and us of sucralfate is described in for example US patent No.3432489 and "The Merck Index" 11th

edition (1989) p1400 entry No 8853.

EP-A-0 403 048 (Warner-Lambert) describes medicated compositions comprising sucralfate and a therapeutically effective amount of a medicament which is, a) substantially water insoluble, or b) a mixture of a water-soluble medicament and a release-delaying material which on admixture forms a substantially water-insoluble medicament. The *in-vitro* testing of a sucralfate/benzoic acid composition against Escherichia coli is described.

US 4,615 697 (Robinson et al.) discloses a controlled release composition comprising an effective amount of a treating agent, which may be a medicament, and a bioadhesive material which is a water-swellable and water-insoluble, fibrous, cross-linked carboxy-functional polymer. The controlled release compositions are described as adhering to the skin or the mucous membranes in the presence of water.

Accordingly, in this further aspect, the present invention relies on the combination or co-administration of an antimicrobial agent which is active against H.pylori selected from the group consisting of cationic antimicrobial agents, for example benzene derivatives such as benzoic acid, benzocaine, hexylresorcinol, benzyl alcohol, dibromopropamidine isethionate, 2,4-dichlorobenzyl alcohol, and hyroxy benzoates including methy-, ethyl-, propyl-, n-butyl-, n-heptyl- and benzyl-p-hydroxy benzoates; phenols such as amylmetacresol, chlorochresol, chloroxylenol, clioquinol, phenol, trichlorophenol and creosote; amines such as hexamine; bis-biguanides such as chlorhexidine gluconate and chlorhexidine hydrochloride; quaternary ammonium compounds such as benzalkonium chloride, cetalkonium chloride, cetyl pyridinium chloride, dequilinium chloride, domiphen bromide and cetrimide; pyrimidines such as hexetidine and hexetidine citrate; glycerol esters such as glycerol monolaurate; dyclonine hydrochloride; miconazole; mupirocin; polynoxylin; povidone iodine; sorbate; and natural products such as garlic and tea tree oil, with one or more substances providing a sustained release and/or prolonged retention of the antimicrobial agent in the stomach, so as to overcome, or at least mitigate, the disadvantages associated with conventionally formulated antimicrobial agents and provide an effective treatment for H.pylori infections of the gastric and duodenal mucosa in humans and domestic animals.

In this furth r aspect, the present invention also provides a pharmaceutical composition comprising one or more such antimicrobial agents ffectiv against H.pylori organisms, and one or more substances providing a sustained release and/or prolonged retention of the antimicrobial agent in the stomach.

The present invention extends to these compositions for use in therapy and to the use of these compositions in the manufacture of a medicament for the treatment of gastric disorders associated with Helicobacter pylori.

The antimicrobial agent may for example be co-formulated, suitably by intimate admixture, with a muco-adherent or bioadhesive substance to form a bioadhesive complex. Such a complex confers the additional benefit of locally targetting the antimicrobial agent to the mucus layer of the stomach wall.

Bioadhesive materials suitable for use in compositions of the present invention include materials, both natural and synthetic, which are capable of adhering to biological surfaces such as mucus membranes. Examples of bioadhesive materials include natural gums and plant extracts and synthetic materials such as sucralfate, cellulose derivatives, acrylic acid and methacrylic acid derivatives, for example cross-linked acrylic and methacrylic acid copolymers available under the Trade Names CARBOPOL and POLYCARBOPHIL.

Antimicrobial agents effective against H.pylori may alternatively be formulated to produce a floating alginate raft within the stomach. Such formulations may include solid and liquid dosage forms, and may be prepared according to processes known to persons skilled in the art, for example as described in GB 2 243 549 A.

Controlled release dosage forms, for example beadlets or granules, optionally encapsulated or compressed to form tablets, also form part of the invention. Advantageously, beadlets or granules are coated, layered, or form an intimate, homogeneous matrix with release-delaying materials. Such dosage forms may be prepared using conventional techniques known in the art.

The composition of the invention may be made up in the form of a swallow tablet, a chewable tablet or a water dispersible tablet. Alternatively it may

be supplied as a water-dispersibl powder, either for dispersion immediately prior to administration or for dispensing in liquid form, as a suspension or as a liquid emulsion. Suitable water-dispersible formulations includ soluble effervescent or non-effervescent powders.

The compositions of the present invention may also contain appropriate additives, for example preservatives, buffering agents, suspending agents, flavourings, bulking agents, binders, adhesives, lubricants, disintegrants, colouring agents, sweeteners, adsorbents, thickeners, suspending agents, and diluents including water, appropriate to their form.

If desired, the release of the antimicrobial agent may be altered by changing its particle size, or by applying a suitable coating particularly to tablet forms. Coatings able to retard the release of pharmaceuticals are well known in the art of pharmaceutical formulation, and include polymers such as acrylic resins (for example the material sold by Rohm Pharma under the trade name 'Eudragit') and cellulose esters (for example ethyl cellulose).

An encapsulated or delayed release formulation according to the invention may be any such form well known in the art. Suitable coating materials include water-based coatings, solvent-based coatings and colloidal dispersions. Lipids may also be used to form liposome-type formulations.

Preferred antimicrobial agents for use in the treatment of gastrointestinal disorders associated with H. pylori are cationic antimicrobial agents, in particular hexetidine and hexetidine citrate, chlorhexidine gluconate and chlorhexidine hydrochloride, benzalkonium chloride, dequilinium chloride, cetyl pyridinium chloride, cetrimide, and domiphen bromide.

The antimicrobial agent is present in compositions of the invention in an appropriate amount to provide an effective dose, which will depend on the pharmacological properties of the compound employed. Normally a single dose used to treat an adult human will provide from 0.01mg to 100mg, generally 0.1 to 15mg of antimicrobial agent.

For example, a suitable singl dose of chlorhexidin hydrochloride lies in the range of 0.1 to 100 mg, typically 1.0 to 15mg. A suitable single dose for cetylpyridinium chloride li s in th range 0.01 to 100 mg, typically 0.1 to

10mg.

For compositions containing sucralfate as muco adherent, a suitable single dose lies in the range 0.5 to 20g, typically 1.0 to 8.0g.

The compositions of the present invention may also include additional therapeutic agents useful in the treatment of peptic ulcers and gastritis, and agents which delay gastric emptying, for example methylcellulose, guar gum, fats such as triglyceride esters, and triethanolamine myristate.

Compositions of the invention may be administered as often as a physician directs, having regard to the severity of the H.pylori infection. Normally, it is recommended to take a dose two or three times daily, advantageously after meals.

Surprisingly, it has also been found that the activity of the antimicrobial agents hereinbefore identified against Helicobacter pylori may be enhanced if these agents are administered in combination with various materials which are not recognised as antimicrobial agents per se, for example chelating agents, surfactants and mixtures thereof.

Accordingly, antimicrobial agents and compositions containing antimicrobial agents as hereinbefore described for use in the treatment of Helicobacter pylori, further comprising a chelating agent, a surfactant or mixtures thereof also form part of the invention.

Suitable chelating agents include alkyldiamine tetraacetates, for example ethylenediaminetetraacetic acid (EDTA), CaEDTA, and $CaNa_2EDTA$, EGTA and citrate.

Suitable surfactants include ionic and non-ionic surfactants. Examples of non-ionic surfactants include glycerides and the materials commercially available under the Trade Names Tweens and Tritons. Ionic surfactants include fatty acids and quaternary compounds, the anionic surfactant sodium dodecyl sulphate, and amphoteric surfactants such as cocamidopropyl betaine and emulsifiers.

The compositions of the invention may be prepared by conventi nal

pharmaceutical techniques. Thus the composition may, for example, be prepared by mixing together the required ingredients with stirring or grinding to ensure adequate dispersion. Alternatively, some of the ingredients may be mixed together before other ingredients are added. Granulation and/or coating techniques may be used at a convenient stage in the process if required.

The invention will now be illustrated by the following examples.

Example 1

Activity of Cationic Antimicrobial Agents against Helicobacter Pylori

The Minimum Inhibitory Concentration (MIC) of representative antimicrobial agents of the invention against human strains of H.pylori (H.pylori NCTC 11916 & 11637) were assessed using a spiral plater and automatic agar plate pourer, according to the method of Wallace A.S. and Corkill J.E. (J. Microbiol. Methods, 10, 303-310, 1989).
MIC values were calculated according to the equation for the Archimedes spiral.

	MIC Value (mg/l)		Kill Time (mins)
Compound	NCTC 11916	NCTC 11637	
benzalkonium chloride	0.496	0.32	> 30
cetrimide	1.217	1.217	> 30
chlorhexidine HCl	3.33	3.81	> 30
dequilinium chloride	1.217	0.716	< 30
glycerol monolaurate	2.16	1.828	< 30
hexetidine citrate	2.69	2.25	< 5
hexetidine	1.887	1.851	< 1
mupirocin	0.058	0.079	> 30
cetyl pyridinium chloride	0.175	0.168	< 1
domiphen bromide	0.93	0.66	< 30
n-heptyl-p-OH-benzoate	16.5	12.3	< 1
hexyl resorcinol	2.96	2.63	> 30
amylmetacresol	1.49	5.97	

Example 2

Formulation Examples

A. A tablet prepared according to standard methods including chlorhexidine hydrochloride (5mg) and sucralfate (1000mg).

B. A tablet prepared according to standard m thods including cetylpyridinium chloride (3mg) and sucralfate (1000mg).

C. An effervescent powder containing per 5g dose:

cetyl pridinium chloride	:	3mg
citric acid (anhydrous)	:	2.2g
sodium bicarbonate	:	2.3g
sodium carbonate	:	0.5g

D. An effervescent powder containing per 5g dose:

domiphen bromide	:	6mg
citric acid (anhydrous)	:	2.2g
sodium bicarbonate	:	2.3g
sodium carbonate	:	0.5g

E. An effervescent powder containing per 5g dose:

chlorhexidine HCL	:	5mg
citric acid (anhydrous)	:	2.2g
sodium bicarbonate	:	2.3g
sodium carbonate	:	0.5g

F. A tablet containing cetyl pyridinium chloride (3mg) and alginate (1.5g).
(Dosage : 2 tablets t.i.d.)

G. A tablet containing domiphen bromide (6mg) and alginate (1.5g).
(Dosage : 2 tablets 6.i.d.)

H. A tablet containing chlorhexidine HCl (5mg) and alginate (1.5g).
(Dosage : 2 tablets t.i.d.)

CLAIMS

1. The use of an antimicrobial agent selected from benzoic acid, benzyl alcohol, dibromopropamidine isethionate, 2,4-dichlorobenzyl alcohol, a hyroxy benzoate, amylmetacresol, chlorochresol, phenol, trichlorophenol, creosote, hexamine, chlorhexidine hydrochloride, benzalkonium chloride, dequilinium chloride, domiphen bromide, cetrimide, hexetidine citrate, glycerol monolaurate, dyclonine hydrochloride, miconazole, mupirocin, polynoxylin, povidone iodine, sorbate, garlic and tea tree oil, for the manufacture of a medicament for the treatment of gastric disorders associated with Helicobacter pylori.

2. The use of an antimicrobial agent selected from benzoic acid, benzocaine, hexylresorcinol, benzyl alcohol, dibromopropamidine isethionate, 2,4-dichlorobenzyl alcohol, a hyroxy benzoate, amylmetacresol, chlorochresol, chloroxylenol, clioquinol, phenol, trichlorophenol, creosote, hexamine, chlorhexidine gluconate, chlorhexidine hydrochloride, benzalkonium chloride, cetalkonium chloride, cetyl pyridinium chloride, dequilinium chloride, domiphen bromide, cetrimide, hexetidine, hexetidine citrate, glycerol monolaurate, dyclonine hydrochloride, miconazole, mupirocin, polynoxylin, povidone iodine, sorbate, garlic and tea tree oil, for the manufacture of a medicament for the treatment of gastric disorders associated with Helicobacter pylori, characterised in that the antimicrobial agent is combined with one or more substances providing a sustained release and/or prolonged retention time of the antimicrobial agent in the stomach.

3. The use of an antimicrobial agent selected from benzoic acid, benzocaine, hexylresorcinol, benzyl alcohol, dibromopropamidine isethionate, 2,4-dichlorobenzyl alcohol, a hyroxy benzoate, triclosan, amylmetacresol, chlorochresol, chloroxylenol, clioquinol, phenol, trichlorophenol, creosote, hexamine, chlorhexidine gluconate, chlorhexidine hydrochloride, benzalkonium chloride, cetalkonium chloride, cetyl pyridinium chloride, dequilinium chloride, domiphen bromide, cetrimide, hexetidine, hexetidine citrate, glycerol monolaurate, dyclonine hydrochloride, miconazole, mupirocin, polynoxylin, povidone iodine, sorbate, garlic and tea tree oil, for the manufacture of a medicament for the treatment of gastric disorders associated with Helicobacter pylori, characterised in that the antimicrobial agent is combined with at least one of a chelating agent or a surfactant.

4. A pharmaceutical compositi n comprising an antimicrobial agent selected from benzoic acid, benzocaine, hexylresorcinol, benzyl alcohol, dibromopropamidine isethionate, 2,4-dichlorobenzyl alcohol, a hyroxy benzoate, amylmetacresol, chlorochresol, chloroxylenol, clioquinol, phenol, trichlorophenol, creosote, hexamine, chlorhexidine gluconate, chlorhexidine hydrochloride, benzalkonium chloride, cetalkonium chloride, cetyl pyridinium chloride, dequilinium chloride, domiphen bromide, cetrimide, hexetidine, hexetidine citrate, glycerol monolaurate, dyclonine hydrochloride, miconazole, mupirocin, polynoxylin, povidone iodine, sorbate, garlic and tea tree oil, and one or more substances providing a sustained release and/or prolonged retention time of the antimicrobial agent in the stomach.

5. A pharmaceutical composition as claimed in claim 4 wherein the one or more substances providing a sustained release and/or prolonged retention time of the antimicrobial agent in the stomach is a muco-adherent or bioadhesive substance.

6. A pharmaceutical composition as claimed in claim 5 wherein the one or more substances providing a sustained release and/or prolonged retention time of the antimicrobial agent in the stomach is a natural gum, a plant extract, sucralfate, a cellulose derivative, or an acrylic acid or methacrylic acid derivative,

7. A pharmaceutical composition as claimed in claim 6 wherein the antimicrobial agent and the muco-adherent or bioadhesive substance are co-formulated as an intimate mixture.

8. A pharmaceutical composition comprising an antimicrobial agent selected from benzoic acid, benzocaine, hexylresorcinol, benzyl alcohol, dibromopropamidine isethionate, 2,4-dichlorobenzyl alcohol, a hyroxy benzoate, triclosan, amylmetacresol, chlorochresol, chloroxylenol, clioquinol, phenol, trichlorophenol, creosote, hexamine, chlorhexidine gluconate, chlorhexidine hydrochloride, benzalkonium chloride, cetalkonium chloride, cetyl pyridinium chloride, dequilinium chloride, domiphen bromide, cetrimide, hexetidine, hexetidine citrate, glycerol mon laurate, dyclonine hydrochloride, miconazole, mupirocin, polynoxylin, povidone iodine, sorbate, garlic and tea tree il, and at least one of a chelating agent or a surfactant.

9. A pharmaceutical composition as claimed in claim 8 wherein the chelating agent is ethylenediaminetetraacetic acid (EDTA), CaEDTA, and $CaNa_2EDTA$, EGTA or citrate.

10. A process for preparing a pharmaceutical composition as claimed in any one of claims 5 to 9 comprising the admixture of the antimicrobial agent with one or more substances providing a sustained release and/or prolonged retention time of the antimicrobial agent in the stomach, and/or at least one of a chelating agent or a surfactant, and a pharmaceutically acceptable carrier.